

Amendments to Claims, and Listing thereof:

This listing of claims will replace all prior versions, and listings, of claims in the application:

1-85. Canceled.

86. (Previously Presented) A method of determining the presence of anti-Factor VIII allo-antibodies capable of degrading Factor VIII in a mammal, which comprises:

- i) isolating the plasma from a sample of blood taken from said mammal,
- ii) isolating anti-Factor VIII allo-antibodies from said plasma;
- iii) placing said anti-Factor VIII allo-antibodies in contact with Factor VIII for a period of time sufficient to permit any degradation of said Factor VIII by said anti-Factor VIII allo-antibodies; and
- iv) determining, after said period of time, whether said Factor VIII has been degraded by said anti-Factor VIII allo-antibodies.

87. (Previously Presented) The method of claim 86, wherein in step ii), said anti-Factor VIII allo-antibodies are isolated from said plasma by combining them with said Factor VIII.

88. (Previously Presented) The method of claim 87, wherein said Factor VIII is coupled to a matrix.

89. (Previously Presented) The method of claim 86, wherein in step ii), said anti-Factor VIII allo-antibodies are isolated by affinity chromatography.

90. (Previously Presented) The method of claim 89, wherein in step ii), said affinity chromatography comprises the use of Factor VIII covalently coupled to a Sepharose matrix.

91. (Previously Presented) The method of claim 90, wherein said Sepharose matrix is activated with cyanogen bromide.

92. (Previously Presented) The method of claim 86, wherein in step iii), said Factor VIII is labelled with a labelling agent.

93. (Previously Presented) The method of claim 92, wherein said labelling agent is a radio-labelling agent.

94. (Previously Presented) The method of claim 93, wherein said radio-labelling agent is ¹²⁵I.

95. (Previously Presented) The method of claim 86, wherein in step iii), said Factor VIII is placed in contact with the anti-Factor VIII allo-antibodies for a period of time of between about 0.5 and about 30 hours, at a temperature of about 15 to about 40°C.

96. (Previously Presented) The method of claim 86, wherein in step iii), said Factor VIII is placed in contact with the anti-Factor VIII allo-antibodies for a period of time of about 10 hours, at a temperature of about 15 to about 40°C.

97. (Previously Presented) The method of claim 86, wherein in step iii), said Factor VIII is placed in contact with the anti-Factor VIII allo-antibodies for a period of time of between about 0.5 and about 30 hours, at a temperature of 38°C.

98. (Previously Presented) The method of claim 86, wherein in step iii), said Factor VIII is placed in contact with the anti-Factor VIII allo-antibodies for a period of time of about 10 hours, at a temperature of 38°C.

99. (Previously Presented) The method of claim 86, wherein step iv) is carried out by a determination comprising a separation technique and a visualisation technique.

100. (Previously Presented) The method of claim 99, wherein said separation technique is selected from the group consisting of gel electrophoresis, and gel filtration.

101. (Previously Presented) The method of claim 100, wherein said gel electrophoresis is SDS PAGE.

102. (Previously Presented) The method of claim 100, wherein said gel filtration is fast protein liquid chromatography gel filtration.

103. (Previously Presented) The method of claim 100, wherein said visualisation technique is autoradiography.

104. (Previously Presented) The method of claim 86, which further comprises :
characterising the site(s) in said Factor VIII molecule cleaved by said anti-Factor VIII allo-antibodies.

105. (Previously Presented) The method of claim 104, wherein said characterisation is carried out by placing said Factor VIII in contact with said anti-Factor VIII allo-antibodies capable of degrading Factor VIII, separating and then sequencing the fragments of Factor VIII resulting therefrom.

106. (Previously Presented) The method of claim 105, wherein said separation is carried out using a gel electrophoresis technique.

107. (Previously Presented) The method of claim 106, wherein said separation is SDS PAGE.

108. (Previously Presented) The method of claim 105, wherein said sequencing is carried out using an N-terminal sequencing technique.

109. (Previously Presented) The method of claim 108, wherein said sequencing carried out using an N-terminal sequencing technique is by using an automatic protein microsequencer.

110. (Currently Amended) The method of claim [[1045]] 105, wherein said sequencing locates scissile bonds : Arg³⁷²-Ser³⁷³, located between the A1 and A2 domains, Tyr¹⁶⁸⁰-Asp¹⁶⁸¹, located on the N-terminus of the A3 domain, and Glu¹⁷⁹⁴-Asp¹⁷⁹⁵ located within the A3 domain of the Factor VIII molecule.

111. (Currently Amended) An isolated amino acid sequence consisting of:

SEQ. ID No. 1: Ser Val Ala Lys Lys His Pro.

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112. (Currently Amended) An isolated amino acid sequence consisting of:

SEQ. ID No. 2: Asp Glu Asp Glu Asn Gln Ser.

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113. (Currently Amended) An isolated amino acid sequence consisting of:

SEQ. ID No. 3: Asp Gln Arg Gln Gly Ala Glu.

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114. (Previously Presented) A peptide or non-peptide analogue of an amino acid sequence of claim 111, which is capable of inhibiting any site in the Factor VIII molecule which is susceptible to being lysed by an anti-Factor VIII allo-antibody.

115. (Previously Presented) A peptide or non-peptide analogue of an amino acid sequence of claim 112, which is capable of inhibiting any site in the Factor VIII molecule which is susceptible to being lysed by an anti-Factor VIII allo-antibody.

116. (Previously Presented) A peptide or non-peptide analogue of an amino acid sequence of claim 113, which is capable of inhibiting any site in the Factor VIII molecule which is susceptible to being lysed by an anti-Factor VIII allo-antibody.

117. (Previously Presented) A method of neutralising catalytic anti-Factor VIII allo-antibodies comprising using an anti-Factor VIII allo-antibody-catalysed Factor VIII degradation inhibitor.

118. (Previously Presented) The method of claim 117, wherein said inhibitor comprises a protease inhibitor.

119. (Previously Presented) The method of claim 118, wherein said protease inhibitor is 4-(2-aminoethyl)benzenesulphonyl fluoride hydrochloride.

120. (Previously Presented) The method of claim 117, wherein said inhibitor inhibits cleavage of the scissile bonds : Arg³⁷²-Ser³⁷³, located between the A1 and A2 domains, Tyr¹⁶⁸⁰-Asp¹⁶⁸¹, located on the N-terminus of the A3 domain, and Glu¹⁷⁹⁴-Asp¹⁷⁹⁵ located within the A3 domain of the Factor VIII molecule.

121. (Previously Presented) The method of claim 117, wherein said inhibitor comprises a peptide or non-peptide analogue of the isolated amino acid sequence:

SEQ. ID No. 1: Ser Val Ala Lys Lys His Pro.

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122. (Previously Presented) The method of claim 117, wherein said inhibitor comprises a peptide or non-peptide analogue of the isolated amino acid sequence:

SEQ. ID No. 2: Asp Glu Asp Glu Asn Gln Ser.

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123. (Previously Presented) The method of claim 117, wherein said inhibitor comprises a peptide or non-peptide analogue of the isolated amino acid sequence:

SEQ. ID No. 3: Asp Gln Arg Gln Gly Ala Glu.

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124-140. Canceled.

141. (Previously Presented) An anti-Factor VIII allo-antibody-catalysed Factor VIII degradation inhibitor, which comprises a peptide or non-peptide analogue of the isolated amino acid sequence:

SEQ. ID No. 1: Ser Val Ala Lys Lys His Pro.

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142. (Previously Presented) An anti-Factor VIII allo-antibody-catalysed Factor VIII degradation inhibitor, which comprises a peptide or non-peptide analogue of the isolated amino acid sequence:

SEQ. ID No. 2: Asp Glu Asp Glu Asn Gln Ser.

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143. (Previously Presented) An anti-Factor VIII allo-antibody-catalysed Factor VIII degradation inhibitor, which comprises a peptide or non-peptide analogue of the isolated amino acid sequence:

SEQ. ID No. 3: Asp Gln Arg Gln Gly Ala Glu.

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144-150. Canceled.

151. (Previously Presented) An isolated anti-Factor VIII allo-antibody, which has a catalytic activity capable of catalysing degradation of Factor VIII.

152. (Previously Presented) An isolated anti-Factor VIII allo-antibody which is obtainable by the method of claim 86.

153. (Previously Presented) The isolated anti-Factor VIII allo-antibody of claim 151, which cleaves the following scissile bonds in the Factor VIII molecule: Arg³⁷²-Ser³⁷³, located between the A1 and A2 domains, Tyr¹⁶⁸⁰-Asp¹⁶⁸¹, located on the N-terminus of the A3 domain, and Glu¹⁷⁹⁴-Asp¹⁷⁹⁵ located within the A3 domain of the Factor VIII molecule.

154. (Previously Presented) The isolated anti-Factor VIII allo-antibody of claim 152, which cleaves the following scissile bonds in the Factor VIII molecule: Arg³⁷²-Ser³⁷³, located between the A1 and A2 domains, Tyr¹⁶⁸⁰-Asp¹⁶⁸¹, located on the N-terminus of the A3 domain, and Glu¹⁷⁹⁴-Asp¹⁷⁹⁵ located within the A3 domain of the Factor VIII molecule.